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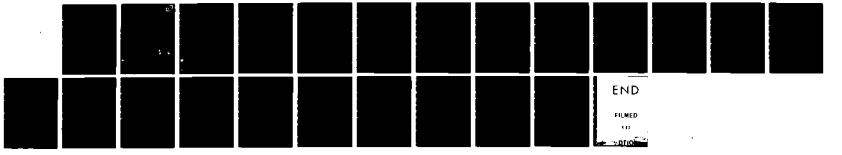

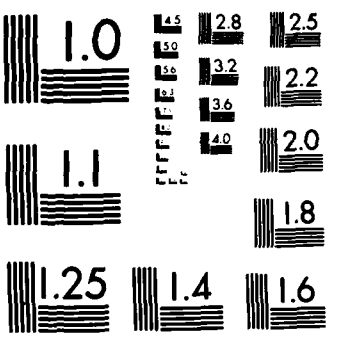

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Acute mountain sickness (AMS) is a syndrome which occurs when unacclimatized individuals rapidly ascend to hign altitude. It is postulated that cerebral edema causes the symptoms of AMS. Since dexamethasone is useful in treating some forms of cerebral edema, we investigated its role in the prevention of AMS. Utilizing a double-blind, crossover design, eight young men were exposed to a simulated altitude of 4570 m (15,000 ft) on two occasions. On one occasion, they received dexamethasone (4 mg every 6 h) for 36 h before and throughout the 42 h exposure. On the other, they received a placebo.

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Presence of AMS symptoms was established by a questionnaire and a clinical interview. Indices of cerebral and respiratory symptoms (AMS-C and AMS-R, respectively) were derived from the questionnaire. During the clinical interview, subjects were scored from 0 (no symptoms) to 3 (severe symptoms). Dexamethasone significantly reduced AMS symptoms. AMS-C decreased from (mean ± SE) 1.09 ± .18 to 0.26 ± .08 and AMS-R decreased from 0.64 ± .09 to 0.31 ± .06 during dexamethasone treatment (both $p < .0001$). As judged by clinical interview, symptom score decreased from 1.10 ± .11 to 0.28 ± .07 ($p < .0001$). We conclude that dexamethasone is effective in preventing the symptoms of AMS.

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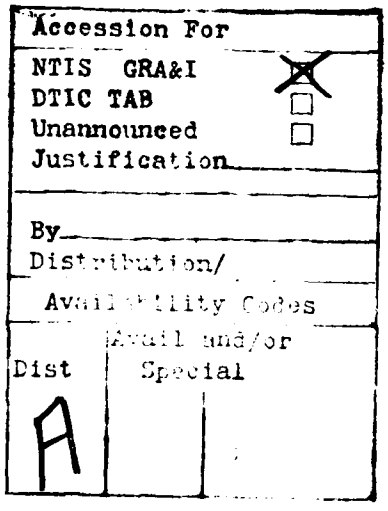
Human subjects participated in these studies after giving their free and informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on Use of Volunteers in Research.



PREVENTION OF ACUTE MOUNTAIN SICKNESS BY DEXAMETHASONE

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ABSTRACT

Acute mountain sickness (AMS) is a syndrome which occurs when unacclimatized individuals rapidly ascend to high altitude. It is postulated that cerebral edema causes the symptoms of AMS. Since dexamethasone is useful in treating some forms of cerebral edema, we investigated its role in the prevention of AMS. Utilizing a double-blind, crossover design, eight young men were exposed to a simulated altitude of 4570 m (15,000 ft) on two occasions. On one occasion, they received dexamethasone (4 mg every 6 h) for 36 h before and throughout the 42 h exposure. On the other, they received a placebo. Presence of AMS symptoms was established by a questionnaire and a clinical interview. Indices of cerebral and respiratory symptoms (AMS-C and AMS-R, respectively) were derived from the questionnaire. During the clinical interview, subjects were scored from 0 (no symptoms) to 3 (severe symptoms). Dexamethasone significantly reduced AMS symptoms. AMS-C decreased from (mean $\pm$ SE) 1.09 $\pm$ .18 to 0.26 $\pm$ .08 and AMS-R decreased from 0.64 $\pm$ .09 to 0.31 $\pm$ 0.06 during dexamethasone treatment (both $p < .0001$). As judged by clinical interview, symptom score decreased from 1.10 $\pm$ .11 to 0.28 $\pm$ .07 ($p < .0001$). We conclude that dexamethasone is effective in preventing the symptoms of AMS.

INTRODUCTION

Acute mountain sickness (AMS) is a syndrome characterized by headache, nausea, vomiting, insomnia, and lassitude. These symptoms occur over 1 to 5 days when lowlanders ascend to high altitude (1,2,3). Acetazolamide (4) and staging (spending time at an intermediate altitude) (5) have been recommended for the prevention of AMS, but are only partially effective. With increasing numbers of individuals visiting altitude for recreation and other pursuits, a reliable, completely effective prophylactic therapy for AMS would be of great value.

The precise pathophysiology of AMS is unknown (6,7); however, evidence suggests that a derangement in fluid homeostasis at altitude may cause cerebral edema, which leads to the symptom complex. Two lines of indirect evidence favor this hypothesis. First, AMS is part of a spectrum of illness induced by acute altitude exposure. This spectrum includes high altitude pulmonary edema (HAPE) and high altitude cerebral edema (HACE). AMS symptoms overlap these two other entities; indeed, patients may exhibit components of all three syndromes, although one tends to predominate (8). Second, investigators have found peripheral and periorbital edema in association with AMS (9) and have measured shifts in the distribution of body water from the extra- to intracellular space in subjects exposed to altitude (10). These findings suggest alterations in fluid balance which might also affect the central nervous system and lead to brain edema. Direct evidence implicating cerebral edema in AMS was the demonstration by Singh (1) that 34 subjects with AMS had elevations in cerebrospinal fluid pressure which resolved as the illness improved.

Hypoxia accompanying terrestrial altitude exposure could potentially give rise to either cytotoxic (hypoxic) or vasogenic cerebral edema (11,12). Cytotoxic edema is unlikely to occur except under conditions of extreme altitude exposure

because the oxygen supply to the brain is maintained by increased cerebral blood flow as long as arterial O_2 saturation remains above 70% ($\leq$ 5000 m altitude) (13). Under conditions of increased cerebral blood flow, vasogenic cerebral edema, however, is quite likely. A 33% increase in cerebral blood flow has been demonstrated by Severinghaus et al. (14) in subjects acutely exposed to an altitude of 3800 m. This hyperperfusion occurs despite the mitigating influence of altitude-induced hypocapnic alkalosis. Lassen and Harper (15) have hypothesized that increases in cerebral blood flow may be sufficient to overwhelm cerebral autoregulation, cause an increase in filtration through the cerebral microcirculation and result in extracellular cerebral edema.

Dexamethasone is a potent synthetic glucocorticoid with demonstrated efficacy in the management of vasogenic cerebral edema of diverse etiologies (11). It has been recommended for the treatment of HACE (2,16) although never systematically evaluated for this purpose. To our knowledge, there have been no controlled trials utilizing this drug for the treatment or prevention of AMS. We hypothesized that, if mild vasogenic cerebral edema arising from altitude exposure were responsible for the symptoms of AMS, then dexamethasone might be an effective prophylactic treatment for this illness. To test this hypothesis, eight volunteers were administered dexamethasone or placebo and then exposed to a simulated altitude of 4570 m (15000 ft) in a hypobaric chamber. The results of this trial indicate that dexamethasone prevented the syndrome of AMS.

METHODS

Subjects

The subjects were healthy male soldiers (age 20-26 years) residing at sea level. Potential subjects were excluded if they had any recent (within 6 months) exposure to altitude, current physical illness, or medical contraindication to the administration of dexamethasone or altitude exposure. All gave their informed consent to participate.

Altitude Exposure

Twelve subjects completed the first altitude exposure. Four of these did not participate in the crossover phase. Three withdrew voluntarily, and the fourth was excluded because of a viral illness. Thus, a total of eight subjects were exposed to simulated altitude on two separate occasions. During one exposure, a subject was administered a capsule containing 4 mg of dexamethasone every 6 hours. On the other, he received an identical capsule containing lactose. Neither the test subjects nor the investigators were aware of which treatment was being administered. The study began at 2200 h on day 1 when the subjects were given the first dose of drug or placebo. At 2200 h on day 2, the subjects entered the altitude chamber which was maintained at sea level while baseline measurements were performed. At 2200 h on day 3 the chamber was evacuated to a barometric pressure of 427 torr (equivalent to an altitude of 4570 m). The subjects remained at this simulated altitude for the next 42 h. At the end of that time, they were returned to ambient barometric pressure and the medication was discontinued. Three weeks after the first exposure, the subjects were crossed over to the other treatment, and repeated the same altitude exposure.

The altitude chamber in which the exposures took place is a 1066 cubic meter stainless steel facility consisting of two separate compartments connected by an airlock, which enables free passage of personnel and supplies to the subjects during the study without affecting the pressure of the study compartments. Temperature and relative humidity within the chamber were maintained at $22 \pm 1^{\circ}C$ and $40 \pm 3\%$, respectively, throughout the experimental period.

Assessment of Symptoms

Assessment of the presence of AMS was accomplished with the Environmental Symptoms Questionnaire (ESQ) which was administered to the subjects twice on the first day of chamber occupancy at sea level and five times while the chamber was at simulated altitude. This 67-question symptom inventory has been used to quantitate symptoms during exposure to diverse environmental stresses, including heat, cold and altitude exposure (17). A digital computer was utilized to administer the ESQ. Subjects responded to statements which appeared on the cathode ray tube (CRT) of the computer. To quantify symptoms or feelings, 6 phrases were used: "not at all"; "slight"; "somewhat"; "moderate"; "quite a bit"; "extreme". Each phrase was used in a sentence describing a subjective feeling. As an example, six sentences exploring the symptom "thirsty" would appear simultaneously on the CRT, ranging from "I do not feel thirsty" to "I feel extremely thirsty." To record a response, the subject moved the cursor in front of the sentence which most accurately described his feeling at that point in time, and pressed the "enter" key. The next set of symptom sentences would then automatically appear on the CRT. The computer was programmed to check consistency of responses. If inconsistencies were found, it printed a message on the CRT at the end of the test instructing the subject to read the questions more carefully and "try again." The ESQ was then automatically readministered. This method of testing offered the advantages of rapid data analysis, high test subject attention and cooperation, and checks on internal consistency and reliability during each administration. A value of from 0 ("not at all") to 5 ("extreme") was assigned to each of the 67-symptom responses. To assess the degree of AMS, two derived scores were calculated. One was a weighted average of "cerebral" symptoms, labeled AMS-C, and the other a weighted average of "respiratory" symptoms, AMS-R. The former score

was derived from such symptoms as "headache", "nausea", and "insomnia", while the latter reflects symptoms like "shortness of breath" and "rapid heart beat". Previous studies (18) have established the validity of these measures of AMS and have indicated that a criterion score value of 0.7 for AMS-C and 0.6 for AMS-R reliably identifies those individuals who report the experience of being "sick".

A clinical interview was conducted by one of the investigators (PR). The interviewer was unaware of the subject's ESQ responses or score. On the basis of the presence and degree of symptoms, the subjects were graded for severity of AMS using the following scale: 0 (well), 1 (mildly ill), 2 (moderately ill), and 3 (severely ill). At the time of the interview, each subject had his blood pressure and pulse rate measured in the supine and standing positions.

Respiratory and Chemical Measurements

Resting minute ventilation and respiratory frequency, oxygen consumption, carbon dioxide production and respiratory quotient were determined at 1430 h, once at sea level (day 2) and twice at altitude (days 3 and 4). Measurements were made with the subject seated comfortably and breathing through a mouthpiece connected to a Koegal valve. Expired air was directed through low resistance tubing into a mixing chamber. The volume of expired air was measured with a Pneumoscan spirometer (KL Engineering), with its transducer located within the expired air line. Volumes were automatically corrected to BTPS. Samples of air from the mixing chamber were analyzed for oxygen (Oxygen analyzer, model S-3A, Applied Electrochemistry, Inc.) and carbon dioxide (LB2, Beckman Instruments). The computed values for oxygen consumption and carbon dioxide production were corrected to STPD. Measurements were made over a 7-minute period. The first 2 minutes were used to flush the system and to allow the subjects to relax. Expired volume was measured from minutes 3 through 7. Respiratory frequency was recorded 2 to 4

times within this period. Mixed expired O_2 and CO_2 were recorded at minute 5.5. Tidal volume was calculated by dividing minute ventilation by the average frequency.

Each morning prior to the subjects' arising, venous blood samples were drawn for the determination of hemoglobin, hematocrit, electrolytes, urea nitrogen, glucose, and cortisol. The last was measured by the competitive protein-binding method of Murphy (19). Urine output was measured on each subject every 12 hours beginning on 2000 h on day 1 of the st . Body weight was measured each morning upon arising.

Retinal Photography

Photographs were made of each subject's right retina at 1500 h on days 2, 3 and 4 using a retinal camera (TRE-FE, Topcon). To ensure consistent magnification, these were taken at a constant distance from the cornea. The developed negatives were projected on a screen and the width of the superior temporal artery was measured at one disc diameter from the optic disc using calipers.

Statistics

Normally distributed data were examined with analysis of variance. If significant differences were found, Newman-Keuls test (20) was used to compare multiple samples. Data obtained from the ESQ and physician's assessment were not normally distributed. For these data, Friedman's rank sum test was utilized for analysis (20). Significance was accepted for p values < 0.05.

RESULTS

Dexamethasone markedly reduced symptoms of AMS as assessed both by the ESQ and by the clinical interview (Figure 1). ESQ scores at sea level were low and were unaffected by the administration of drug. During altitude exposure, ESQ scores were significantly higher with placebo administration

compared to dexamethasone, reflecting an increased incidence of AMS symptoms while taking placebo. Dexamethasone treatment was associated with a decrease in AMS-C from 1.09 $\pm$ .18 to 0.26 $\pm$ .08 (mean $\pm$ SE; $p < 0.0001$) and in AMS-R from 0.64 $\pm$ .09 to 0.31 $\pm$ .06 ($p < 0.0001$; Figure 1). Dexamethasone administration reduced the average symptom score from above to below the previously established criterion values (0.7 for AMS-C, 0.6 for AMS-R) for "sick" individuals.

The physician's clinical assessment of acute mountain sickness also identified a significant salutary effect of dexamethasone (Figure 1). There was a reduction in sickness score from 1.10 $\pm$ .11 during placebo treatment to 0.28 $\pm$ .07 ($p < 0.0001$) during dexamethasone treatment. Particularly evident was the improvement in the symptoms of anorexia and headache.

Minute ventilation was increased at altitude, but there was no difference between placebo (18.0 $\pm$ 2.6 L/min) and dexamethasone (19.1 $\pm$ 3.4 L/min) treated subjects. A mild weight loss was observed but was also not significantly different between groups (0.95 $\pm$ .34 vs 0.09 $\pm$ .26 kg, placebo vs dexamethasone). No differences were observed between groups in mixed expired O_2 or CO_2 concentration, O_2 consumption, CO_2 production, blood pressure, pulse rate, or postural blood pressure changes.

Dexamethasone treatment reduced a.m. plasma cortisol from 17.8 $\pm$ 2.6 to 2.1 $\pm$ 0.3 µg/dl on day 1 and from 13.4 $\pm$ 2.4 to 2.0 $\pm$ 0. µg/dl (both $p < .001$) on day 2 of altitude.

Dexamethasone was associated with an increase in urine output during altitude exposure (Figure 2). Whereas 5 of the 8 subjects receiving placebo exhibited a decrease in urine output, 7 of 8 subjects receiving dexamethasone had an increase in urine output during the first 24 h of altitude exposure. No direct measures of body fluid compartments were performed. Indirect measures,

such as body weight, hematocrit, and electrolytes, did not suggest any difference between placebo and dexamethasone treatment at altitude.

The results of the retinal photography are displayed in Figure 3. All subjects demonstrated an increase in retinal arterial diameter at altitude, consistent with an increase in retinal and cerebral blood flow (21). Dexamethasone-treated subjects exhibited a smaller retinal artery diameter throughout the study, although this difference achieved statistical significance only on day 2 of altitude exposure.

DISCUSSION

In this study the administration of dexamethasone prevented the symptoms of AMS in young men acutely exposed to a simulated altitude of 4570 m. The two independent methods that we used to assess the presence of AMS both demonstrated a highly significant reduction in symptoms during dexamethasone treatment.

The benefit of dexamethasone is even more striking if one examines individual subject's responses to altitude exposure. Five of the individuals in our study developed significant symptoms of AMS (AMS-C > 0.7) while on placebo; all 5 demonstrated improvement on dexamethasone treatment. Furthermore, none of the 3 subjects who were minimally symptomatic while taking placebo developed increased symptoms on dexamethasone. Thus, despite the high dose of dexamethasone used in this study, its effects were largely confined to the amelioration of AMS symptoms.

Both the physician conducting the interviews and the subjects themselves were blind to the administration of the drug. Consequently, observer or reporter bias cannot explain the results of the trial. The order of administering the drugs was also randomly allocated, so that no effect of chamber familiarity would confound the results. In addition, the four subjects who completed the first

exposure, but did not participate in the crossover, were evenly divided between drug and placebo. Thus, this unplanned loss of subjects did not alter the proportion of subjects receiving the drug in the second half of the study.

The mechanism by which dexamethasone exerted the observed beneficial effect is not known. A nonspecific effect of dexamethasone which may have masked symptoms, but did not alter underlying pathophysiology, cannot be excluded as the explanation for these results. If this were the case, then one would anticipate that as altitude exposure progresses, symptoms or complications would emerge despite dexamethasone treatment. This trial may have been too brief to observe these complications. On the other hand, specific actions of dexamethasone may explain our results. The drug appeared to modify the dilatation observed in the retinal vessels during altitude exposure; dexamethasone-treated subjects had less vasodilatation on the second day of exposure than those on placebo. If one accepts that AMS symptoms are caused by hypoxia-induced cerebral edema, this relative vasoconstriction may have lessened the accumulation of cerebral edema. It might also have alleviated any rise in cerebrospinal fluid pressure by diminishing cerebral blood volume (11). An additional possibility is that dexamethasone may have prevented edema formation by exerting an effect on the microcirculation to prevent vascular leak under conditions of high blood flow (22).

Another observed difference which might be suggestive of the mechanism was the response of urinary output to altitude. Most of the subjects experienced an increase in urine output during the first 24 h of altitude exposure while taking dexamethasone. During placebo administration, most showed a decline in urine output (Figure 2). It is possible that dexamethasone may have had a mild diuretic effect. Diuresis has been observed in patients undergoing neurosurgery if they were pretreated with dexamethasone (23). It has also been observed that

an antidiuresis correlates with the severity of AMS (1), and conversely, mountain lore has it that diuresis upon exposure to altitude (the so-called "Hohendiurese" of alpinists) is associated with diminished symptoms of AMS (24).

No differences were observed in any of the measures of respiratory function. Although arterial blood gases were not measured, the similarities between groups in respiratory parameters suggest that dexamethasone did not work by altering ventilatory drive or severity of hypoxia.

In summary, administration of dexamethasone prevented the symptoms of acute mountain sickness during exposure to simulated altitude. This study supports the hypothesis that AMS arises from cerebral edema. Additional studies will be necessary to define the benefits and risks of dexamethasone for the prevention of acute mountain sickness.

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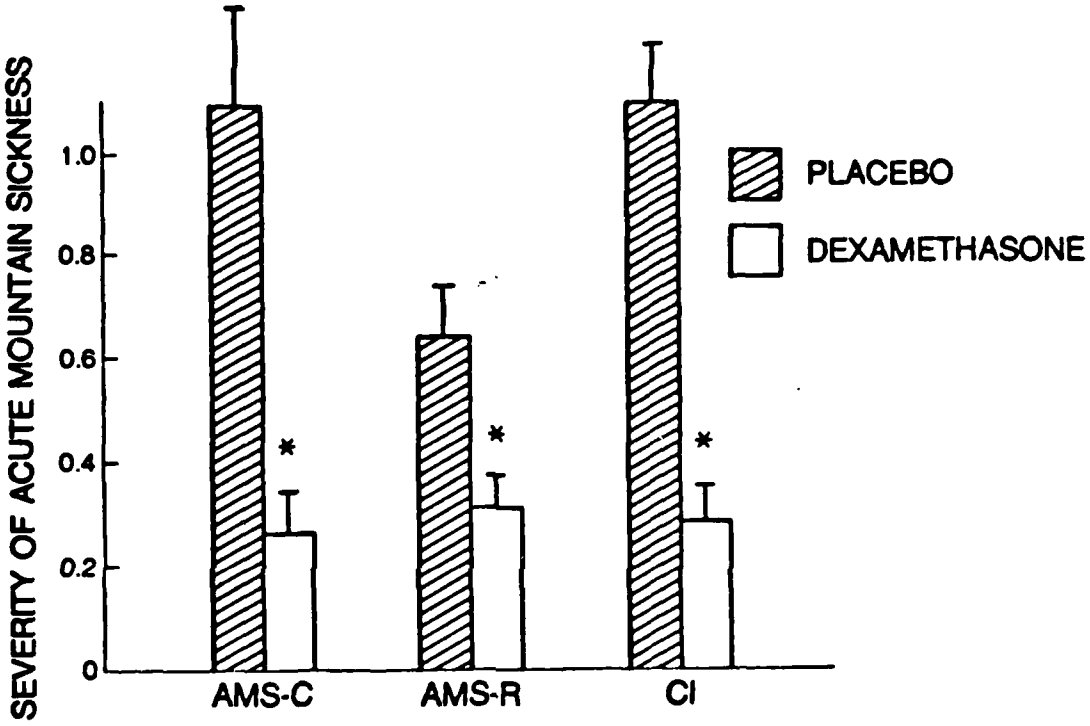

Figure 1. Effect of dexamethasone on severity of acute mountain sickness (AMS). Data are presented as means + SE. AMS-C and AMS-R are scores derived from the Environmental Symptoms Questionnaire (ESQ) (18). CI represents scores obtained on a physician's clinical interview. *$p < 0.001$ for comparisons between dexamethasone and placebo treatment.

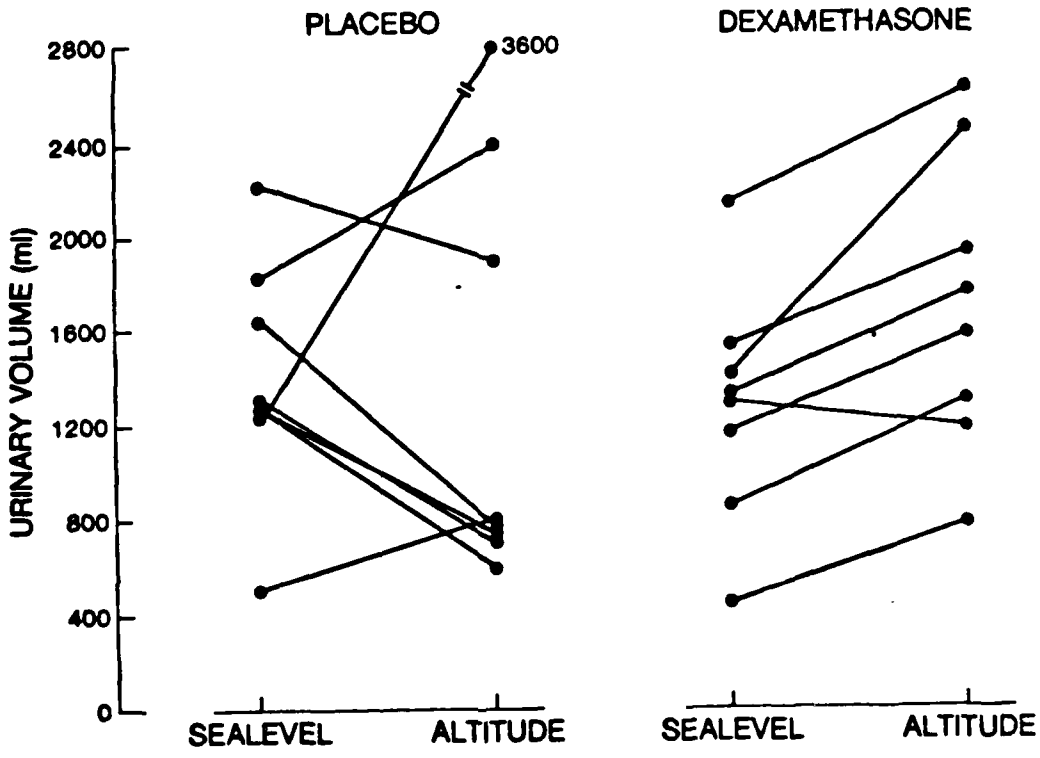

Figure 2. Twenty-four urinary output collected at sea level and 4570 m simulated altitude while taking dexamethasone or placebo. Lines connect the values for consecutive 24-hour periods for each individual.

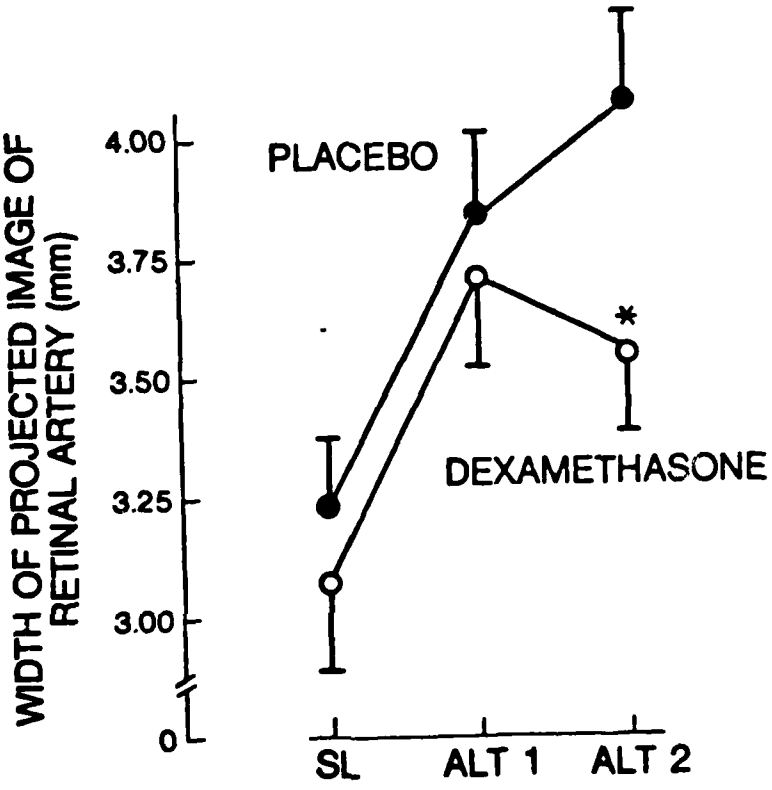

Figure 3. Mean width of superior temporal retinal artery image at sea level (SL) and after 16 hours (ALT 1) and 36 hours (ALT 2) of exposure to a simulated altitude of 4570 m. Data are for eight subjects exposed on two occasions, once while taking dexamethasone (open circles) and once while taking placebo (closed circles). Mean value $\pm$ S.E. as shown. * $p < .001$.

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